What impact has mandatory folic acid fortification had on the incidence of neural tube defects in the US and Canada?

Conclusion

Strong and consistent evidence demonstrates a large reduction in the incidence of neural tube defects (NTDs) in the US and Canada following mandatory folic acid fortification.

Grade: Strong

Overall strength of the available supporting evidence: Strong; Moderate; Limited; Expert Opinion Only; Grade not assignable For additional information regarding how to interpret grades, click here.

Evidence Summary Overview

Of the 13 studies, nine of the studies were conducted in the United States and four were conducted in Canada. All studies, with the exception of one, was of neutral quality. Given the ecologic nature of mandatory fortification, it was impossible to conduct a controlled trial during this time.

Three of the US studies (Besser et al, 2007; Chen et al, 2008; Forrester et al, 2005) were conducted in single states: Arkansas, California, and Hawaii, respectively. All other US studies were conducted in multiple states or nationally represented using several different population-based birth registries. Only two of the studies did not demonstrate a decline inneural tube defects (NTD) post-fortification (Besser et al, 2007; Chen et al, 2008). Both of these trials were conducted in a single state: Arkansas and California, respectively. The study of Mosely et al, 2007 conducted in Arkansas is of poor quality as it investigated a statewide folic acid supplementation trial during the transition to mandatory folic acid grain fortification; therefore, there is serious confounding, and it is not possible to fully ascertain the effects of the grain fortification vs. folic acid supplementation.

Of the four Canadian studies, one was conducted in Nova Scotia (Persad et al, 2002), one in Alberta (Godwing et al, 2008) and the other two were in seven of ten Canadian provinces (De Wals et al, 2007 and 2008). It appears that the two studies of De Wals et al (2007 and 2008) are the same cohort All of the Canadian studies demonstrated a decline in NTDs. Similarly, it appears that the studies of Williams et al (2002 and 2009) used data from the same 24 population-based birth defect surveillance programs.

Only De Wals et al (2007 and 2008) and Williams et al (2002 and 2009) examined the NTD trends before fortification, during optional fortification and post-fortification in Canada and the United States, respectively. Only the studies of De Wals et al (2007 and 2008) demonstrated a continued reduction in NTD going from optional to mandatory fortification. The studies of Williams et al (2002 and 2009) demonstrated the reduction in NTD from pre- to mandatory fortification. They did not show a difference between optional fortification and mandatory fortification. The study of Williams et al, 2009, also examined the NTD reductions by race and ethnicity. The prevalence of spina bifida (SB) decreased 36% among Hispanic births, 34% among non-Hispanic white births and 19% for black births from pre- to post-fortification. The decline in the prevalence of anencephaly

(AN) was similar among Hispanic births and non-Hispanic white births. No significant decline in AN was observed in non-Hispanic black births during this time.

In summary, these data demonstrate strong and consistent temporal reductions in NTD in children following mandatory folic acid fortification in the United States and Canada that took place in the late 1990s. In the United States, the reduction is between 23% to 54% for SB and 11% to 16% for AN. In Canada, the reduction is approximately 53% for SB and 31% for AN. It is important to note that it is possible that other factors could have contributed to the trends observed in these trials. Awareness of the importance of folic acid supplementation for women of childbearing years was heightened during this time. Similarly, women may have increased the consumption of other foods high in folate during this time. Due to the ecologic nature of mandatory folic acid fortification in the US and Canada, further analysis of the different contributions to the causes of the NTD decline will need to be established, to fully understand the unique contributions of folic acid fortification of flour and uncooked cereals.

Evidence Summary Paragraphs

Besser et al, 2007 (neutral quality), in a cross-sectional study, used data from the Metropolitan Atlanta Congenital Defects Program (MACDP) to identify birth defects among infants and fetuses of at least 20 weeks of gestation. Three periods were considered: 1)1968 to 1981, when prenatal diagnosis was rarely used, 2) 1981 to 1993, when the use of prenatal diagnosis was increasing in Atlanta but MACDP did not ascertain prenatal diagnoses, and 3) 1994 to 2003, when prenatal diagnosis was used in Atlanta and MACDP during folic acid fortification. During January 1, 1968 to December 31, 2003, 434 infants and fetuses were identified with AN and 663 with SB. Total prevalence of both AN and SB declined during this time. Estimates of the annual percent change (APC) in prevalence of AN were: -6.9% (95% CI: -10.0, -3.6) for period 1; -2.9% (95% CI: -7.9, 2.3) for period 2; and -6.8% (95% CI: -12.6, -0.7) for period 3. Estimates of the APC in prevalence for SB were -7.1% for period 1, -7% for period 2 and -6.2% for period 3. The 95% confidence intervals around the APC for all three periods overlapped, indicating no significant (NS) variation in the point estimates of the slopes. This analysis suggested that changes in AN and SB surrounding folic acid fortification could be part of pre-existing trends.

Canfield et al, 2005 (neutral quality), in a trend study, assessed the effect of fortification on NTD rates. For 16 birth defects categories selected for the study, birth prevalence for two time periods was calculated with data submitted from 23 states in 1995 to 1996 (pre-fortification) and 1999 to 2000 (post-fortification), Of the 23 participating programs, eight conducted case ascertainment among pregnancy terminations. For most of the conditions studied, a decline in prevalence was observed comparing the 1999 to 2000 to the 1995 to 1996. Among other conditions AN (PR=0.84, 95% CI: 0.76, 0.94) and SB (PR=0.66, 95% CI: 0.61, 0.71) had statistically significant declines. The reductions in prevalence were two to three percentage points greater among the programs with prenatal data. Prevalence ratios appeared to vary for some defects depending on the programs' availability of prenatal ascertainment. The significant declines for SB and AN were observed in both groups of registries.

CDC Report, 2004 (neutral quality), conducted a noncomparative descriptive report using data from 23 population-based surveillance systems that included prenatal ascertainment of these birth defects from two 24-month periods (pre-fortification period: 1995 to 1996 and post-fortification period: 1999 to 2000). The estimated number of NTD-affected pregnancies in the US declined from 4,000 in 1995 to 1996 to 3,000 in 1999 to 2000. After fortification, there was a 27% decline in NTD-affected pregnancies among systems with prenatal ascertainment and a 26% decline among systems without prenatal ascertainment. 1,180 fetal deaths (occurring at less than 20 weeks) or elective terminations occurred before fortification, compare with 840 after fortification.

Chen et al, 2008 (neutral quality), in a trend study, compared the slopes of two regression lines that summarized the annual change in NTD prevalence before (pre-fortification slope) and after (post-fortification slope). Data selected all deliveries in eight central California counties, reported as vital statistics and affected pregnancies identified by birth defects surveillance between January 1, 1989 and December 31, 2003. Two periods were considered: Pre-fortification period (January 1, 1989 to September 30, 1996) Post-fortification period (October 1, 1998 to December 31, 2003). From this data, 690 NTD cases were reported among 886,985 deliveries, as well as 420 SB and 270 AN cases. The average prevalence over the entire study period for all NTDs was 77.8 cases per 100,000 deliveries, and 30.4 and 47.4 cases per 100,000 deliveries for AN and SB respectively. For all NTD combined, the slopes showed that prevalence were decreasing by 7.5 (slope: -7.5; 95% CI: -12.4, -2.5) cases per 100,000 deliveries per year before fortification, whereas NTD prevalence were no longer decreasing after fortification. Comparison of the differences of the two slopes showed that the fortification slope exceeded the pre-fortification slope by 12.6 (95% CI: 2.6, 22.6) cases per 100,000 deliveries per year. Prevalence ratios for all NTDs combined and for AN and SB separately were less than one, suggesting that the post-fortification prevalence were lower than the pre-fortification prevalence. Estimates for NTDs overall and for AN were significant (upper confidence=1.00) and the estimate for SB was not significant (upper confidence limit=1.1).

De Wals et al, 2007 (neutral quality), in a retrospective cohort study evaluates baseline rates of NTDs on seven Canadian provinces from 1993 to 2002, and the magnitude of the decrease after folic acid fortification. From the data, 2,446 subjects with NTD were identified; 60% of pregnancies affected with NTDs were terminated after prenatal diagnosis (SB 53% and AN 34%). The overall ratio of AN to SB was 0.65, and there was no significant (NS) variation of this ratio during the study years. Prevalence of NTDs showed a stable pattern rate from 1993 through 1997, followed by a decrease from 1998 through 2000 and stabilization thereafter. There was no significant downward trend during the pre-fortification years from 1993 through 1997, either in the whole data set or in any of the participating provinces. Overall prevalence of NTDs at birth decreased from 1.58 per 1000 births before fortification to 0.86 per 1,000 births during the full-fortification period, a 46% reduction (RR=0.54; 95% CI: 0.49, 0.60). The magnitude of the decrease was higher for SB (53%) than for either AN (38%, P=0.02) or encephalocele (31%, P=0.03). Also, the data showed a gradient between the east-to-west in the pre-fortification rates of defects and in the magnitude of rate reduction after fortification was fully implemented.

De Wals et al, 2008 (neutral quality), in a retrospective study, assessed the impact of fortification policy on the frequency of NTDs. The study included live-births, stillbirths, and termination of pregnancies because of fetal anomaly to women resident in seven Canadian provinces, from 1993 to 2002. Data were divided in three periods: 1) all births ending before September 30, 1997 [belonging to the pre-fortification period (N=970,191)], 2) those between October 1, 1997 and March 31, 2000 [belonging to a partial fortification period (N=455,889)], and 3) those after this date [occurring during the full fortification period (N=487,034)]. A total of 1,286 SB cases were identified (51% live-births, 3% stillbirths and 46% terminations). The overall prevalence rate of SB decreased from 0.86 per 1,000 during the pre-fortification period to 0.57 per 1,000 during the partial fortification period and to 0.40 per 1,000 during full fortification period (P for linear trend <0.0001). The multivariate analysis showed the effect of fortification in reducing the proportion of upper defects remained while controlling for the region and for the type of birth (OR=0.56; 95% CI: 0.34, 0.91; P=0.02 for the partial fortification vs. pre-fortification period and for the full fortification period vs. pre-fortification period (OR=0.31, 95% CI: 0.16, 0.60; P<0.001).

Forrester et al, 2005 (neutral quality), in a trend study examined the potential impact of folic acid fortification on the rates of selected birth defects using data from a population-based birth defects registry in Hawaii. Data from 1986 to 2002 were divided in two periods, and two trends were examined. The first set was 1986 to 1996 (pre-fortification) and 1999 to 2002 (mandatory fortification). The second set was 1993 to 1996 (pre-fortification) and 1999 to 2002 (mandatory fortification), thus using equal lengths of time both before and after fortification. Results for the first set of data showed that birth defects rate had declined after folic acid fortification by 10% and 100% for all but three of the birth defects categories. The decline was not statistically significant for NTDs. For the second set, all but three of the defects categories showed a decline in rate after folic acid fortification. Among those, NTD (R=0.64; 95% CI: 0.44, 0.93), and SB (R=0.58; CI: 0.35, 0.96) were statistically significant.

Godwin et al, 2008 (neutral quality), in a trend study assessed changes in birth prevalence of select structural congenital anomalies between pre-fortification (1992 to 1996) and post-folic acid fortification (1999 to 2003) of grain products using data from Canada-based Alberta Congenital Anomalies Surveillance System (ACASS). Significant decreases in the birth prevalence of SB (OR=0.51, 95 % CI: 0.36, 0.73) during the post-fortification period. Birth prevalence decreases for AN were not statistically significant.

Honein et al, 2001 (neutral quality), in a trend study, evaluated the impact of food fortification with folic acid on NTD birth prevalence. Data from the National Study of Birth Certificate Data for live births to women in 45 US states and Washington, DC, between January 1990 and December 1999 were divided in two periods: Before fortification (October 1995 through December 1996) compared with after mandatory fortification (October 1998 through December 1999). The birth prevalence of NTDs reported on birth certificates decreased from 37.8 per 100,000 live births before fortification to 30.5 per 100,000 live births conceived after mandatory folic acid fortification, representing a 19% decline (PR=0.81;95% CI: 0.75 to 0.87). During the same period, NTD birth prevalence declined from 53.4 per 100,000 to 46.5 per 100,000 (PR=0.87; 95% CI: 0.64, 1.18) for women who received only third-trimester or no prenatal care.

Mosley et al, 2007 (negative quality), in a population-based longitudinal study, assessed the rates of NTDs in Arkansas per 10,000 live births. Data from the Arkansas Reproductive Health Monitoring System (ARHMS), which monitored birth defects among Arkansas women, showed that the use of supplements was 32%. Rates of NTDs declined from 11.9 per 10,000 births in 1994 to 1995 to 7.2 per 10,000 live births in 2002 to 2003. In summary, NTDs in Arkansas has declined 40% since intervention programs (supplementation and fortification) were implemented.

Mosley et al, 2007 (neutral quality), in a population-based longitudinal cohort study, evaluated the rates of NTDs. Data from the Arkansas Reproductive Health Monitoring System (ARHMS) monitored birth defects among Arkansas women, and identified eligible birth defects among live-born or stillborn infants, miscarriages or electively terminated pregnancies. The data were divided in two periods: 1) 1994 to 1995 and 2) 2002 to 2003. Among Arkansas residents, supplement use was 32%; rates of NTDs declined from 11.9 per 10,000 births in 1994 to 1995 to 7.2 per 10,000 live births in 2002 to 2003. Among Hispanic births the most recent rate (10 per 10,000 births per year) was about half the rate (19.8 per 10,000 births per year) before public health interventions. Among whites, NTD rates per 10,000 births declined from 13.5 per year to 8.7. Rates per 10,000 births for blacks had increased slightly (5.8 to 6.6) but not statistically significant. In summary, NTDs in Arkansas have declined 40% since intervention programs (supplementation and fortification) were implemented.

Persad et al, 2002 (neutral quality) in a retrospective cohort study evaluated the annual incidence of all open NTDs, including those occurring in stillbirths and terminated pregnancies, in Nova Scotia over a 10-year period (1991 to 2000). The period spans times before and after folic acid supplementation initiatives and before and after folic acid fortification of grain products was implemented. Comparing pre- vs. post-fortification periods (1991 to 1997 vs. 1998 to 2000), incidence declined for open NTDs, including SB and AN. Open NTDs fell 54%, from 2.58 per 1,000 births on average during 1991 t o1997 to 1.17 per 1,000 births during 1998 to 2000 (RR=0.46, 95% CI: 0.32 to 0.66, P<0.001). Mean annual incidence of SB decreased from 1.51 before to 0.62 per 1,000 births after folic acid fortification (RR=0.40, 95% CI: 0.25 to 0.67, P<0.001). Mean annual incidence of AN decreased from 0.93 before to 0.38 per 1,000 births after folic acid fortification (RR=0.41, 95% CI: 0.22 to 0.77, P=0.004). In summary, fortification of grain products in Nova Scotia resulted in a significant reduction in the incidence of NTDs.

Williams et al, 2002 (neutral quality), in a trend study, evaluated data from 24 population-based birth defects surveillance programs (nine programs with and 13 without prenatal ascertainment). The study identified 5,630 cases of SB and AN. The data was divided in three categories: Before folic acid fortification (January 1995 to December 1996), optional fortification (January 1997 to September 1998) and mandatory fortification (October 1998 to December 1999). The prevalence of SB and AN during the pre- to the mandatory fortification period decreased 31% for SB (PR=0.69, 95% CI: 0.63, 0.74) and 16% for AN (PR=0.84, 95% CI: 0.75, 0.95). The prevalence of SB decreased 40% (PR=0.60, 95% CI: 0.51, 0.71) among the nine programs with prenatal ascertainment, and 28% (PR=0.72, 95% CI: 0.65, 0.80) among the 13 programs without prenatal ascertainment. No decline was observed from the optional to the mandatory fortification period. In conclusion, the decline in the prevalence of SB was temporally associated with folic acid fortification.

Williams et al, 2005 (neutral quality), in a trend study, evaluates prevalence of SB and AN among racial or ethnic groups during the transition to mandatory folic acid fortification in the US. The study included 4,468 cases of SB and 2,625 cases of AN from 21 population-based birth defects surveillance systems. Also, the data (1995 to 2002) were divided in three periods: Pre-fortification period (January 1995 to December 1996), optional fortification period (January 1997 to September 1998) and the mandatory fortification period (October 1998-December 2002). Prevalence ratio (PR) were calculated by dividing the prevalence from the mandatory fortification by the prevalence in the pre-fortification period. The prevalence of SB decreased 36% among Hispanic births from the pre-fortification to the mandatory fortification period (PR=0.64; 95% CI: 0.56, 0.74), 34% among non-Hispanic white births (PR= 0.66; 95% CI: 0.60, 0.72) and 19% for black births (PR=0.81; 95% CI: 0.67, 1.00). The decline in the prevalence of AN was similar among Hispanic births (PR: 0.74; 95% CI: 0.62, 0.88) and non-Hispanic white births (PR=0.71; 95% CI: 0.63, 0.80). No significant decline was observed among non-Hispanic black births.

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Author, Year, Study Design, Class, Rating	**Population/Sample Description**	**Measurements or Intervention**	**Significant Outcomes**

Besser LM, Williams LJ et al, 2003 Study Design: Trend Study Class: D Rating:	Data from the Metropolitan Atlanta Congenital Defects Program (MACDP) identified birth defects among infants and fetuses of at least 20 weeks of gestation. Periods considered: 1. 1968 to 1981 (prenatal diagnosis was rarely used) 2. 1981 to 1993 (use of prenatal diagnosis was increasing in Atlanta) 3. 1994 to 2003 (prenatal diagnosis was used during folic acid fortification).	Prevalence of AN and SB for three time periods (plotted number of infants and fetuses with AN or SB per 10,000 live-births and determined slope of line regression). The slope as defined as the annual percent Δ in AN or SB prevalence. Prevalence of AN and SB during each prenatal ascertainment period for the following: Pregnancy outcome, sex, mother's race, gravidity and mother's age.	During January 1, 1968 to December 31, 2003 434 infants and fetuses were identified with AN and 663 with SB. Total prevalence of both AN and SB ↓ during this time. Estimates of the annual percent Δ (APC) in prevalence of AN were: -6.9% (95% CI: -10.0, -3.6) for period 1; -2.9% (95% CI: -7.9, 2.3) for period 2; and -6.8% (95% CI: -12.6, -0.7). Estimates of the APC in prevalence for SB were -7.1% for period 1, -7% for period 2 and -6.2% for period 3. The 95% CIs around the APC for all three periods overlapped, indicating NS variation in the point estimates of the slopes.
CDC, 2004 Study Design: Non-comparative descriptive report Class: D Rating:	Total US births derived from National Vital Statistics System, and data from 23 population-based surveillance systems that include prenatal ascertainment of these birth defects from two 24-month periods: • Pre-fortification period (1995 to 1996) • Post-fortification period (1999 to 2000).	The number of NTD-affected pregnancies and births determined as prevalence multiplied by the average total number of U.S. births during pre-fortification and post-fortification years. Fetal deaths and elective pregnancies Systems with prenatal ascertainment: Estimated total	The estimated number of NTD-affected pregnancies in the US ↓ from 4,000 in 1995 to 1996 to 3,000 in 1999 to 2000. After fortification, there was a 27% ↓ in NTD-affected pregnancies among systems with prenatal ascertainment and a 26% decline among systems without prenatal ascertainment. 1,180 fetal deaths (occurring at less than 20 weeks) or elective terminations occurred

		Estimated total number of pregnancies, including live births, stillbirths, prenatally diagnosed cases and elective terminations.	before fortification, compare with 840 after fortification.
Canfield M, Collins J et al, 2005 Study Design: Trend study Class: D Rating:	Data from 23 state registries during the time periods: • 1995 to 1996 • 1999 to 2000.	Δs in birth prevalence between the two time periods were assessed by calculating prevalence ratios and 95% CIs for 16 birth defects.	Of the 23 participating programs, eight conducted case ascertainment among pregnancy terminations. For most of the conditions studied, a ↓ in prevalence was observed comparing the 1999 to 2000 to the 1995 to 1996 date ranges. Among other conditions, AN (PR=0.84, 95% CI: 0.76 to 0.94) and SB (PR=0.66, 95% CI: 0.61 to 0.71) had statistically significant declines. The reductions in prevalence were two to three percentage points greater among the programs with prenatal data. Prevalence ratios appeared to vary for some defects, depending on the programs' availability of prenatal ascertainment. The significant declines for SB and AN were observed in both groups of registries.
Chen B, Charmichael S et al, 2008 Study Design: Trend study	All deliveries in eight central California counties, reported as vital statistics and affected pregnancies identified by birth defects surveillance between	Compared the slopes of two regression lines that summarized the annual change in NTD prevalence	690 NTD cases were reported among 886,985 deliveries, as well as 420 SB and 270 AN cases. The average prevalence over the entire study period for

Class: D Rating:	January 1, 1989 and December 31, 2003. Two periods were considered: • Pre-fortification period (January 1, 1989 to September 30, 1996) • Post-fortification period (October 1, 1998 to December 31, 2003).	before (pre-fortification slope) and after (post-fortification slope). Prevalence ratios (PR) were calculated by dividing the overall prevalence in the post-fortification period by that of the pre-fortification period.	all NTDs was 77.8 cases per 100,000 deliveries and 30.4 and 47.4 cases per 100,000 deliveries for AN and SB, respectively. For all NTD combined, the slopes showed that prevalence were ↓ by 7.5 (slope: -7.5; 95% CI: -12.4, -2.5) cases per 100,000 deliveries per year before fortification, whereas NTD prevalence were no longer ↓ after fortification. Comparison of the differences of the two slopes showed that the fortification slope exceeded the pre-fortification slope by 12.6 (95% CI: 2.6, 22.6) cases per 100,000 deliveries per year. Prevalence ratios for all NTDs combined and for AN and SB separately were less than one, suggesting that the post-fortification prevalence were lower than the pre-fortification prevalence. Estimates for NTDs overall and for AN were significant (upper confidence = 1.00) and the estimate for SB was NS(upper confidence limit = 1.1)
De Walls P, Tairou F et al, 2007 Study Design: Trend Study	Live-births, stillbirths and terminations of pregnancies because of fetal anomalies among women residing in seven of the 10 Canadian provinces from 1993 to	Baseline rates of NTDs on each province and the magnitude of the ↓ after folic acid fortification.	2,446 subjects with NTD were identified. 60% of pregnancies affected with NTDs were terminated after prenatal

Class: D Rating:	2002.		diagnosis, as well as SB 53% and AN 34%. The overall ratio of AN to SB was 0.65, and there was NS variation of this ratio during the study years. Prevalence of NTDs showed a stable pattern rate from 1993 through 1997, followed by a ↓ from 1998 through 2000 and stabilization thereafter. There was a NS downward trend during the pre-fortification years from 1993 through 1997, either in the whole data set or in any of the participating provinces. Overall prevalence of NTDs at birth ↓ from 1.58 per 1,000 births before fortification to 0.86 per 1,000 births during the full-fortification period, a 46% reduction (RR=0.54; 95% CI: 0.49 to 0.60). The magnitude of the ↓ was higher for SB (53%) than for either AN (38%, P=0.02) or encephalocele (31%, P=0.03). Also, the data showed a gradient between the east-to-west rates of defects and in the magnitude of rate reduction after fortification was fully implemented.
De Wals P, Tairou F et al, 2008 Study Design: Retrospective	The study included live-births, stillbirths and termination of pregnancies because of fetal anomaly to women resident in seven Canadian provinces, from	Prevalence rates were calculated as the sum of SB cases in live-births, stillbirths and induced abortions,	A total of 1,286 SB cases were identified (51% live-births, 3% stillbirths and 46% terminations). The overall prevalence rate of SB ↓ from 0.86 per

cohort study Class: B Rating:	1993 to 2002. Data were divided in three periods: 1. Births ending before September 30, 1997 [belonging to the pre-fortification period (N=970, 191)] 2. Those between October 1, 1997 and March 31, 2000 [belonging to a partial fortification period (N=455,889)] 3. Those after this date [occurring during the full fortification period (N=487,034)].	divided by total live- and stillbirths. Theoretical birth date was calculated for each NTD case assuming 40 weeks gestation [date of birth or abortion (gestation length in weeks + 40 weeks)], since a large proportion of NTD-affected pregnancies were terminated.	1,000 during the pre-fortification period, to 0.57 per 1,000 during the partial fortification period, and to 0.40 per 1,000 during full fortification period (P for linear trend < 0.0001). The multivariate analysis, the effect of fortification in reducing the proportion of upper defects remained while controlling for the region and for the type of birth (OR=0.56; 95% CI: 0.34, 0.91; P=0.02 for the partial fortification vs. pre-fortification period, and for the full fortification period vs. pre-fortification period (OR=0.31, 95% CI: 0.16, 0.60; P<0.00.1).
Forrester MB and Merz RD, 2005 Study Design: Trend study Class: D Rating:	Data collected from the Hawaii Birth Defects Program (HBDP) and active statewide population-based birth defects registry. Two trends were examined: • The first set was 1986 to 1996 (pre-fortification) and 1999 to 2002 (mandatory fortification) • The second set was 1993 to 1996 (pre-fortification) and 1999-2002 (mandatory fortification). Thus, using equal lengths of time, both before and	Rates for each birth defect were calculated for each time period, using denominators derived from birth certificates. Rates from mandatory fortification were compared to the corresponding pre-fortification rate by calculating rate ratios and 95% CIs.	Results for the first set of data showed that birth defect rate had ↓ after folic acid fortification by 10% and 100% for all but three of the birth defects categories. The decline was NS for NTDs. For the second set, the pre-fortification period was considered from 1993 to 1996, all but three of the defects categories showed a decline in rate after folic acid fortification. In this case, the reduction in NTDs (R=0.64; 95% CI: 0.44, 0.93) and SB (R=0.58; CI: 0.35, 0.96) was statistically significant.

	after fortification.		
Godwin KA, Sibbald B et al, 2008 Study Design: Trend Study Class: D Rating:	Data from the Canada-based Alberta Congenital Anomalies Surveillance System (ACASS) up to one year of age from numerous sources. Two periods were considered: • 1992 to 1996 (pre-fortification) • 1999 to 2003 (post-fortification).	Δs in birth prevalence of select structural congenital anomalies between pre- and post-folic acid fortification of grain products.	N=389,349 live-births and stillbirths (198,321 in 1992 to 1996 and 191,028 in 1999 to 2003). Significant ↓ in SB prevalence (OR 0.51; 95 % CI: 0.36, 0.73; P<0.003) were observed during the post-fortification period. Birth prevalence ↓ for AN were NS. Abortion data was excluded from the analysis.
Honein MA, Paulozzi LJ et al, 2001 Study Design: Trend study Class: D Rating:	National study of birth certificate data for live births to women in 45 US states and Washington, DC, between January 1990 and December 1999.	Birth certificate reports of SB and AN before fortification (October 1995 through December 1996), compared with after mandatory fortification (October 1998 through December 1999).	The birth prevalence of NTDs reported on birth certificates ↓ from 37.8 per 100,000 live births before fortification, to 30.5 per 100,000 live births conceived after mandatory folic acid fortification, representing a 19% ↓ (PR=0.81; 95% CI, 0.75 to 0.87). During the same period, NTD birth prevalence ↓ from 53.4 per 100,000 to 46.5 per 100,000 (PR=0.87; 95% CI: 0.64, 1.18) for women who received only third trimester or no prenatal care.
Mosley B, Hobbs C et al, 2007 Study Design: Population-based longitudinal cohort study	Data from the Arkansas Reproductive Health Monitoring System (ARHMS), monitored birth defects among Arkansas women and identified eligible birth defects	Rates of NTDs in Arkansas cases per 10,000 live births. NTDs included SB and AN.	Among Arkansas residents, supplement use was 32%; rates of NTDs ↓ from 11.9 per 10,000 births in 1994 to 1995 to 7.2 per 10,000 live births in 2002 to 2003.

cohort study Class: B Rating:	eligible birth defects among live-born or stillborn infants, miscarriages or electively terminated pregnancies. The data were divided in two periods: 1. 1994 to 1995 2. 2002 to 2003.		Among Hispanic births, the most recent rate (10 per 10,000 births per year) was about half the rate (19.8 per 10,000 births per year) before public health interventions. Among whites, NTD rates per 10,000 births ↓ from 13.5 per year to 8.7. Rates per 10,000 births for blacks had ↑ slightly (5.8 to 6.6), but NS.
Persad VL, Van den Hoff MC et al, 2002 Study Design: Retrospective cohort study Class: B Rating:	Ten-year period data from January 1, 1991 to December 31, 2000 from live-birth and stillbirth, with open NTDs from the Nova Scotia Atlee Perinatal database and the number of terminated pregnancies affected by NTDs from the Fetal Anomaly database. The data were divided in four periods based on: • Canada's recommendation for pre-conceptional folic acid supplementation in 1994. Comparisons were made between periods before supplementation (1991 to 1994) and after supplementation (1995 to 1997); • Canada's mandatory folic acid fortification of grain products in 1998. Comparison were made between before fortification	Annual incidence of all open NTDs, including those occurring in stillbirths and terminated pregnancies. NTDs included SB, AN and encephaloceles.	Comparing pre- vs. post-supplementation periods (1991 to 1994 vs. 1995 to 1997), there were NS Δs in total annual incidence of open NTDs. The mean annual incidence of NTDs was 2.55 during 1991 to 1994 and 2.61 during 1995 to 1997 per 1,000 births (RR=1.02, 95% CI: 0.77 to 1.35, P=0.87). The mean annual incidence for SB was 1.44 during 1991 to 1994 and 1.60 during 1995 to 1997 per 1,000 births (RR=1.11, 95% CI: 0.79 to 1.60, P=0.64). The mean annual incidence for AN was 1.00 to 0.82 per 1,000 births (RR=0.82, 95% CI: 0.51 to 1.32, P=0.49). Comparing pre- vs. post-fortification periods (1991 to 1997 vs. 1998 to 2000), incidence ↓ for open NTDs, including SB and AN. Open NTDs fell 54%, from 2.58 per 1,000

	(1991 to 1997) and after fortification (1998 to 2000).		births on average during 1991 to 1997 to 1.17 per 1,000 births during 1998 to 2000 (RR=0.46, 95% CI: 0.32 to 0.66, P<0.001). Mean annual incidence of SB ↓ from 1.51 before to 0.62 per 1,000 births after folic acid fortification (RR=0.40, 95% CI: 0.25 to 0.67, P<0.001). The mean annual incidence of AN ↓ from 0.93 to 0.38 per 1,000 births after folic acid fortification (RR=0.41, 95% CI: 0.22, 0.77, P=0.004)
Williams LJ, Mai CT et al, 2002 Study Design: Trend study Class: D Rating:	24 population-based birth defects surveillance programs (nine programs with and 13 without prenatal ascertainment), divided in three categories: • Before folic acid fortification (January 1995 to December 1996) • Optional fortification (January 1997 to September 1998) • Mandatory fortification (October 1998 to December 1999).	Prevalence of SB and AN. Prevalence ratios (PR) calculated dividing prevalence from the mandatory fortification period by the pre-fortification period.	Prevalence of SB and AN from the pre- to the mandatory fortification period ↓: 31% for SB (PR=0.69, 95% CI: 0.63 to 0.74) and 16% for AN (PR=0.84, 95% CI: 0.75, 0.95). The prevalence of SB ↓ 40% (PR=0.60, 95% CI: 0.51, 0.71) among the nine programs with prenatal ascertainment, and 28% (PR=0.72, 95% CI: 0.65, 0.80) among the 13 programs without prenatal ascertainment. No ↓ was observed from the optional to the mandatory fortification period.

			The ↓ in the prevalence of AN remained significant among programs with prenatal ascertainment (PR=0.80, 95% CI: 0.66, 0.97), and programs without prenatal ascertainment showed NS decline (PR=0.85, 95% CI: 0.975, 1.02).
Williams LJ, Rasmussen SA et al, 2005 Study Design: Trend study Class: D Rating:	Data from 21 population-based birth defects surveillance systems (1995 to 2002) were divided in three periods: • Pre-fortification period (January 1995 to December 1996) • Optional fortification period (January 1997 to September 1998) • Mandatory fortification period (October 1998 to December 2002).	Prevalence ratios (PR) were calculated by dividing the prevalence from the mandatory fortification by the prevalence in the pre-fortification period.	The study included 4,468 cases of SB and 2,625 cases of AN. The prevalence of SB ↓ 36% among Hispanic births from the pre-fortification to the mandatory fortification period (PR=0.64; 95% CI: 0.56, 0.74), 34% among non-Hispanic white births (PR= 0.66; 95% CI: 0.60, 0.72) and 19% for black births (PR=0.81; 95% CI: 0.67, 1.00). The ↓ in the prevalence of AN was similar among Hispanic births (PR=0.74; 95% CI: 0.62, 0.88) and non-Hispanic white births (PR=0.71; 95% CI: 0.63, 0.80). NS decline was observed among non-Hispanic black births.

Research Design and Implementation Rating Summary
For a summary of the Research Design and Implementation Rating results, click here.

Worksheets

Besser LM, Williams LJ, Cragan JD. Interpreting changes in the epidemiology of anencephaly and spina bifida following folic acid fortification of the US grain supply in the setting of long-term trends, Atlanta, Georgia, 1968-2003. *Birth Defects Res A Clin Mol Teratol*. 2007 Nov; 79(11): 730-736.

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Williams LJ, Rasmussen SA, Flores A, Kirby RS, Edmonds LD. Decline in the prevalence of spina bifida and anencephaly by race/ethnicity: 1995-2002. *Pediatrics.* 2005; 116: 580-586.